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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,140	12/18/2001	Nigel Dunn-Coleman	GC697	5088
7590 05/14/2004 Genencor International, Inc. 925 Page Mill Road Palo Alto, CA 94034-1013			EXAMINER RAO, MANJUNATH N	
			ART UNIT 1652	PAPER NUMBER
DATE MAILED: 05/14/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,140	DUNN-COLEMAN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17,19,20,22-24 and 26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17,19,20,22-24 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>11-24-03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-17, 19-20, 22-24 and 26 are now currently pending in this application.

Applicants' amendments and arguments filed on 3-5-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous rejection under 35 U.S.C. 112, 2nd paragraph in view of claim amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 and claims 9 and 11 dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 recites the phrase "an expression construct....having at least 85% sequence identity to the amino acid sequence in figure 2, (SEQ I D NO:2)". Applicants are directly comparing the claimed nucleic acid with an amino acid sequence which are structurally and functionally different from each other. Correction is required.

In response tot he same rejection in the previous Office action, applicants have responded by amending the claim. However, applicants have failed to address the above error in the claim. Hence the above rejection is maintained.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19-20, 22, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide isolated from *T.reesei*, with SEQ ID NO:1, 3 encoding a polypeptide with SEQ ID NO:2 having β -glucosidase activity and a method of making said β -glucosidase by transforming a host cell with an expression vector comprising the polynucleotide with SEQ ID NO:3 followed by cultivating the host cells and recovering the expressed β -glucosidase, a recombinant host cell in which the polynucleotide with SEQ ID NO:3 has been inactivated such that it does not express a functional β -glucosidase, does not reasonably provide enablement for a polynucleotide isolated from any or all fungal sources, or a polynucleotide that has 85%, 90%, or 95% identity to the polynucleotide encoding the polypeptide with SEQ ID NO:2 or a polynucleotide (expression vector) comprising polynucleotide that hybridizes under intermediate to high stringency conditions to the polynucleotide encoding polypeptide with SEQ ID NO:2 or to the complementary strand of the same, or encoding a polypeptide having β -glucosidase activity and a method of making said β -glucosidase by transforming a host cell with an expression vector comprising the said polynucleotide followed by cultivating the host cells and recovering the expressed β -glucosidase or a recombinant host cell in which any polynucleotide encoding any β -glucosidase 5 has been inactivated such that it does not express a functional β -glucosidase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

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Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-17, 19-20, 22, 26 are so broad as to encompass any polynucleotide from any fungal source encoding a β -glucosidase, vectors host cells and methods of expressing said β -glucosidase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a given polynucleotide, determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single beta-glucosidase obtained from *T.reesei*. It would require undue experimentation of the skilled artisan to identify and make and use all the claimed polynucleotides. The specification is limited to teaching use of SEQ ID NO: 1 or 3 as a polynucleotide encoding the polypeptide with SEQ ID NO:2. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art

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in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polynucleotides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any polynucleotide with 85%, 90%, or 95% identity to the polynucleotide encoding the polypeptide with SEQ ID NO:2 or polynucleotides that hybridize under intermediate to high stringency conditions to the polynucleotide encoding polypeptide with SEQ ID NO:2 because the specification does not establish: (A) regions of the polynucleotide structure which may be modified without effecting its activity of encoding a functional beta-glucosidase; (B) the general tolerance of said polynucleotide sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide in the polynucleotide with an expectation of obtaining the desired biological

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function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications of SEQ ID NOS: 3. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants have traversed the above rejection arguing that as in the case *In re Bowen*, the Office action fails to suggest any reasons for implication therein that the other described polynucleotides in the specification would not work in the claimed invention. Examiner respectfully disagrees with such a highly misplaced argument. Examiner has clearly given valid scientific reasons for holding the claims as non-enabled. Examiner urges the applicant to go over the rejection once more. Furthermore, Examiner would also like to bring to the attention of the applicant that whatever polynucleotide that may have been described in the specification is not what is being claimed in this invention. Applicant continues the argument that merely objecting that that the claims encompass "extremely large number of polynucleotides" is insufficient and that the "unsupported conjectural statements regarding the undue experimentation are similarly unsupported (it is not exactly clear to the Examiner as to what applicant is intending here) and therefore insufficient to support the

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rejection under 35 U.S.C. § 112, 1st paragraph. Examiner respectfully disagrees with the applicant's conclusion that the rejection is based on conjecture. Examiner has based the rejection on solid scientific reasoning and not on any conjectures as the applicant alleges. In summary, Examiner would like to reiterate that applicants are claiming polynucleotides encoding a β -glucosidase from all fungal sources including mutants, variants and recombinants; variant polynucleotides that are 85-95% identical to SEQ ID NO:1 or 3 and all those polynucleotide^s that are capable of hybridizing under intermediate stringency conditions to the polynucleotide that encodes SEQ ID NO:2. However, the specification does not provide guidance to make the claimed polynucleotides. While methods to produce variants of a known sequence using techniques such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance regarding the specific nucleotides that can be modified without affecting the property of the polynucleotide to encode a polypeptide with β -glucosidase activity as well as methods for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the polynucleotide structure which may be modified without effecting its activity of encoding a

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functional β -glucosidase; (B) the general tolerance of said polynucleotide sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide in the polynucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Finally applicant also argues that claim 1 has been amended to recite polynucleotide encoding β -glucosidase from a fungal source and a β -glucosidase 5 and therefore the rejection must be withdrawn. Examiner respectfully disagrees that even such an amendment would overcome the above rejection. This is because as stated above claims continue to be directed to all fungal polynucleotide encoding β -glucosidases (irrespective of the fact that claim is limited to β -glucosidase 5) including all variants, mutants and recombinants. The support provided in the specification is not enough to enable such a claim. For all the above reasons the above rejection is maintained.

Claims 1, 6-7, 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules encoding beta-glucosidase and a host cell comprising altered β -glucosidase gene such that the gene is inactivated and the production of the β -glucosidase is prevented.

The specification does not contain any disclosure of the structure of all DNA sequences that are encompassed by the claims. The genus of DNAs that comprise these above DNA

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molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicant has not responded to the above rejection. However, Examiner continues to maintain the above rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-7, are rejected under 35 U.S.C. 102(b) as being anticipated by Takashima et al. (J. Biochem., Vol. 125:728-736, 1999). This rejection is based upon the public availability of a printed publication. Claims 1, 6-7, of the instant application are drawn to an isolated polynucleotide derived from a fungal source encoding a β -glucosidase (claim 1), wherein said

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polynucleotide is isolated from a *Trichoderma* source (claims 6-7). Takashima et al. disclose a polynucleotide, encoding a beta-glucosidase, isolated from a fungal source such as a *Trichoderma* sp., Therefore, Takashima et al. anticipate claims 1, 6-7, as written.

In response to the previous Office action, applicants traverse the above rejection arguing that current amended claims are directed to β -glucosidases encoded by polynucleotides having certain enumerated sequences and Takashima does not disclose a polynucleotide with such enumerated sequence. Examiner respectfully disagrees with such an argument. In view of certain claim amendments, Examiner has withdrawn the rejections as applied to claims 19-20, 26. However, the rejection is maintained for the above claims. All that the applicant has done is indicate that the polynucleotide encodes a β -glucosidase 5. However, there are no other structural characteristics of the claimed polynucleotide which can set aside the polynucleotide disclosed in the reference. While the applicant refers to the encoded polypeptide as β -glucosidase 5, the reference discloses a polynucleotide that also encodes a polypeptide with β -glucosidase activity. Takashima discloses a fungal (*Trichoderma*) polynucleotide encoding a polypeptide with β -glucosidase activity. Therefore, contrary to applicants argument, mere recitation of the encoded polypeptide as β -glucosidase 5 does not overcome the above rejection. Therefore the above rejection is maintained.

Conclusion

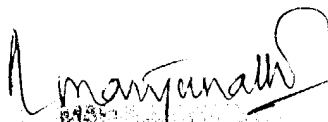
None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
May 7, 2004